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Published in Uranium, Plutonium, Transplutonic Elements Springer-Verlag N.Y., 1973

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Chapter 4

Data on Man

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With 8 Figures

I. Introduction

Animals, not men, are the common experimental subjects in research designed to predict the behavior of radioactive nuclides in man. This is true for uranium quite as much as for other nuclides; witness the abundance of experimental animal data contained in the preceding chapter relative to the amount of information available for presentation in the following pages.

Human data become potentially available when man is exposed either by intent or by inadvertence. The intentional administrations of a radionuclide include the planned experiments designed to gain biological data and the use by physicians for treatment or diagnosis of disease. The inadvertent intakes are experienced either by reason of man's employment or because he lives in a slightly contaminated world. Some of the problems in the collection and use of data from these four sources will be discussed in the following paragraphs.

Planned experiments on man may, for some elements, utilize a short half-life isotope of the element of interest. Such a device enables the experimenter to keep his radiation dose commitment small and yet the amount of the nuclide introduced may be great enough to ensure that the samples collected can be measured at levels well above the sensitivity limits of the analytical methods available. Likewise, because the radiation dose may be made negligible, the experimenter need have no compunction about assembling a volunteer group of normal adult subjects in any convenient age range. The circumstance that a short half-life isotope has been chosen limits the period of observation. While uranium has no such short half-life isotope, the specific activity of natural uranium may be increased by the enrichment, i.e. by increasing the proportion, of ^{235}U (and ^{234}U). The existence of very sensitive analytical methods permits carefully supervised experiments on man. It has been judged prudent to conduct these experiments under hospital conditions with members of the subject group chosen by a physician to be sufficiently alert mentally so that their knowing consent may be obtained, and sufficiently normal physiologically so that the experimental results will be meaningful. Such a group will usually be small and the experimental duration short. The kinds of information that can be obtained are limited by these circumstances.

Several of the long-lived members of the naturally radioactive series have, in the past, been administered orally and intravenously to patients by physicians.

* This author was supported in part by funds from a contract granted to the University of Rochester by the U.S. Atomic Energy Commission and the number UR-3490-191 has been assigned to this chapter.

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At one time or another, uranyl nitrate (between 1890 and 1920), radium bromide or chloride (between 1915 and 1930), and thorium dioxide (between 1930 and 1950) have been administered for a variety of ailments and occassionally with an enthusiasm (FIELD, 1916) which is now regarded by the medical profession as misguided. The quality and the kind of observations recorded by the attending physician should not be expected to satisfy our present quest for precise information and, generally speaking, they do not. In the case of the radium and thorotrast patients much needed information has been gained by remeasurement programs (AUB et al., 1952; NORRIS et al., 1955; SPIESS and MAYS, 1970; LOONEY et al., 1960) using modern detection techniques. No comparable re-study was performed for the uranium-treated patients and the physicians' records constitute the sole source of data.

Information that can be obtained from uranium plant exposures has its own shortcomings. The investigator exercises no control over the circumstances surrounding the introduction of uranium. Information concerning the time of the size and composition of the subject group is often incomplete and sometimes not available to the investigator. Indeed, these data are not only fragmentary, they are in retrospect usually difficult or impossible for the investigator to interpret with confidence.

The fourth source of information, i.e. the study of background uranium in man's food and water and in man himself, has one outstanding advantage: the size of the subject group is limited only by the investigator's time and resources. The obvious disadvantages are the very low concentrations of uranium in nature and the severe demands on measurement techniques. The kinds of information obtainable are restricted. The intakes are derivable in terms of average values rather than individual values. The body distribution data taken from autopsy material are usually interpreted as representing a steady state condition, and yield little or no information on the kinetics of the nuclide's behavior in the body. Since ingestion is the principal route of entry, the background data on uranium do not apply to the industrially important question of lung clearance rates.

It is, therefore, fair to ask "Why consider data on man if they are subject to all these disadvantages? Why not rely entirely on mammalian animal experiments to yield the data needed for control of occupational toxicological hazards?". A review of the basic biological data used by national and international bodies for the calculation of maximum permissible concentrations in air and water for radioactive nuclides (ICRP, Publication 2, 1959) shows that the large majority of listed values depend primarily on animal data. This, however, has not been a matter of choice but of necessity, and the aforesaid values have been listed with the full knowledge that unforeseen differences in the behavior of rats or dogs and man may introduce uncertainties in the calculated protection criteria. It is possible that in some future stage of the art these differences may be predictable and a system of precise extrapolation may be developed. Similarity principles for functional systems in a variety of mammalian species have been studied by interested biologists for many years (i.e. HUXLEY, 1932; ADOLPH, 1949; GÜNTHER and DE LA BARRA, 1966). The generalizations developed by the studies may, on occasion, permit us to "understand" an already identified difference in behavior of a given element in man and in, e.g., a rat, but they do not as yet provide an adequate prediction system. STARA, NELSON, DELLA ROSA, and BUSTAD (1971) addressed themselves to the question of the validity of extrapolating the results of animal research to man. In a review incorporating published data, supplemented by original work, involving a variety of radionuclides and several mammalian species including man, they conclude

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in part that "Careful evaluation of data from several species permit a cautious extrapolation to man. However, the data suggest species specific metabolic pathways for individual isotopes...". The foregoing comments refer to the usefulness of animal data in specifying tissue distribution and excretion for man. An area of equal importance to the radiation toxicologist is that of the dose-injury relationship. The sorts of injury that are considered in the development of occupational air and water limits are those that may develop after tens of years of exposure. If cancer is the injury endpoint, the longer lifespan of man affects the use of animal data in two ways: raising the general question as to whether the incidence and latency of the development of malignancies are related to lifespan and the more specific question as to whether in any given experiment an injury may have been produced but never became manifest because the animal's lifespan was too short.

On the same subject, but with a reservation of a different kind, PARKER (1969), writing on the use of animals to unravel the dose-effect relationship for the radon daughter hazard to the lungs of man, expresses the opinion "On the one side no matter how compelling the animal results, they would be suspect for application to cancer induction in humans. This arises from the growing belief that radiation carcinogenesis requires not only some radiation dose, but some as yet undefined environmental factor...". His further comments define areas of the general problem that require animal experimentation.

The International Commission on Radiological Protection Task Group (ICRP Publication 10, 1968) state in their Introduction that "New (since ICRP Publication 2) data derived from studies of human beings are presented for all these radionuclides except ^{132}Te, ^{144}Ce and ^{239}Np for which the new data pertain to animal experiments...".

There appears to be a consensus among radiation toxicologists that animal data alone are insufficient. Whenever available the use of human data is necessary, sparse and unsatisfactory though they may be, to afford an extra measure of assurance in calculating limits to apply to human exposure.

There is one additional compelling argument for the collection and analysis of data from industrial exposures. It is precisely the consequences of exposure to this aerosol, in this environment, inhaled by these workers, that we hope to control. The experiment in the laboratory may give precise answers given the conditions imposed. To what extent do the conditions reproduce the conditions under which the occupational exposure will occur? To gauge the vulnerability of the laboratory-collected data it must be compared with observations in the industrial situation if such observations exist.

The human data for uranium presented in the following pages appear in three sections: 1) planned experiments organized according to route of administration; 2) data from industrial exposure; and 3) data from background studies.

II. Planned Administrations of Uranium

A. Intravenous Injection

1. The Rochester Intravenous Injection Experiment[1]

(BASSETT, FRENKEL, CEDARS, VAN ALSTINE, WATERHOUSE and CUSSON, 1948)

At the time these experiments were planned the status of the uranium toxicity study was as follows. Animal experiments had shown that severe tubular nephritis

[1] Since this paper has hitherto been available only as University of Rochester Report UR-37 with very limited circulation, a detailed account will be presented here.

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could be produced by large intravenous doses of uranium (LECONTE, 1853; RICHTER, 1905; MACNIDER, 1924). Sensitive methods had been developed to detect early kidney responses by DOUNCE, ROBERTS and WILLS (VOEGTLIN and HODGE, 1949, chap. 14). It had been found that the intravenous injection of 6 μg of U per kg as uranyl acetate produced increased urinary catalase and protein in rabbits and dogs (VOEGTLIN and HODGE, 1949, chap. 14). The view had been developed by DOUNCE (VOEGTLIN and HODGE, 1949, chap. 15) that hexavalent uranium in the blood complexed with bicarbonate, citrate, phosphate and protein, that it was readily filtered by the kidney glomerulus as the bicarbonate and that a large fraction of the dose (60–80 percent) was excreted in the urine in the first 24 hours. A smaller fraction (10–20 percent) was taken up in bone from which it was released only very slowly. With this general picture of the behavior of uranium in animals in mind, BASSETT and others (1948) performed an experiment on human subjects with the following three objectives: 1) to find that dose of soluble uranium salt which, when injected as a single intravenous dose, would produce barely detectable renal injury, 2) to measure the rate at which soluble uranium compounds are excreted after having been introduced into the circulation, and 3) to observe the effect of procedures designed to increase or decrease the elimination rate of uranium.

Six subjects were selected from a large group of hospital patients and transferred to the Metabolic Ward. It is stated that "Criteria of importance in making the selection were reasonably good kidney function with urine free of protein and with a normal sediment on clinical examination. The probability that the patient would benefit from continued hospitalization and medical care was also a factor in the choice". The higher doses were administered to the older patients in order to minimize the remote possibility of late radiation effects. Further protection for patients 5 and 6 was afforded by reducing the specific activity of the enriched uranium by diluting with natural uranium.

To prepare the dose, a uranyl nitrate solution containing ^{238}U, enriched with ^{234}U and ^{235}U, was diluted with a 1.15 percent solution of sodium acetate and adjusted to pH 4.5. After autoclaving and verifying the uranium content, a prescribed volume was injected into the median basilic vein of the patient. Two additional doses each containing the designated volume and prepared in the same way were analyzed for uranium and the average value taken as the patient dose.

Total urine and fecal collection was made from all subjects. Urine was collected as individual voidings on the day of injection and thereafter in pools of 24 hours. Blood specimens were routinely taken for clinical evaluation. Aliquots of urine were wet digested, brought to neutral pH and transferred to an electroplating cell. Plating recoveries were determined to be 95 ± 5 percent. After plating the foil was counted for alpha activity in a low background 2π alpha counter. Fecal samples were analyzed in a similar way after digestion of 1 gram (dry ashed) aliquots of the sample. Blood samples were analyzed in the same way as fecal samples except that 25 ml aliquots were digested.

The uranium used for these experiments was enriched in ^{235}U so that its composition was by weight 29.34 percent ^{238}U, 70 percent ^{235}U and 0.66 percent ^{234}U. This yielded an alpha disintegration rate of about 93 disintegrations per minute per μg of uranium. The authors set their lower limit of measurement at about 0.05 μg which may be translated into from about 0.3 to 1.2 μg per total sample depending on the aliquot to sample ratio.

Renal function tests (VOEGTLIN and HODGE, 1949, chap. 14) included urinary catalase, protein amino nitrogen to creatinine nitrogen ratio, glomerular filtration

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Table 4.1. Patient data and urinary results for the Rochester experiment (BASSETT, FRENKEL, CEDARS, VANALSTINE, WATERHOUSE and CUSSON, 1948)

Patien						Urinary excretion	
no.	sex	age yr.	wt. kg	condition	Dose μg/kg	percent 24 h	percent 5 days
1	m	32	60.5	arthritis-rheumatoid	6.3	82.3	86
2	f	40	75.5	cirrhosis of liver	6.3	84.7	87
3	f	24	37.0	chronic undernutrition	15.8	69.2	71.5
4	m	42	64.0	chronic alcoholism	30.0	66.6	74.3
5	m	51	65.3	unresolved pneumonia	42.0	75.3	76.3[a]
6	m	61	55.1	pulmonary fibrosis	70.9	77.6	87.6
6	m[b]	61	55.1	gastric ulcer	54.5	57.3	79.5

[a] Collected 4 days only.
[b] A second dose was given to this patient.

Table 4.2. Summary of renal function tests on Rochester patients. (Taken from BASSETT et al., 1948)

Patient no.	1	2	3	4	5	6
Urinary catalase (ml of H_2O)	no change[a]	no change	no change	no change	3.6 (3.7)[b]	9.5 (10.5)[c]
Urinary protein (mg albumin/5 ml urine)	0(0)	0(0)	0(0)	0(20)[d]	0(<5)[e]	
Amino N/Creat. N	no change	0.49 (0.48)	0.26 (0.24)	no change	0.15 (0.11)	0.14 (0.16)
Glom. filtration (ml/min)	—	115 (118)	118 (117)	—	—	99 (93)
Renal plasma flow (ml/min)	—	463 (402)	593 (638)	—	—	482 (499)
Max. tub. excr. cap. (mg/min)	—	70 (79)	—	—	—	95 (83)
Urea clearance (percent normal)	102 (96)	—	43 (52)	—	77 (—)	—

[a] To be read "tests were performed and no change observed". Dash to be read, "test was not performed".
[b] Except as noted average pre-injection values are listed first with average post-injection values in parentheses.
[c] Questionably positive values on days 4 and 5.
[d] Not an average. Listed value occurred on day 4.
[e] Not an average. Traces, <5 mg, noted on days 5 and 6.

(mannitol), renal plasma flow, maximum tubular excretory capacity (para aminohippuric acid) and urea clearance. Not all of the more complicated tests were performed on every patient; however, urinary catalase and protein were followed carefully in each case.

Size of Single Dose Versus Renal Function. Table 4.1 presents pertinent data on the subjects and the dose of hexavalent uranium administered. Table 4.2 presents the results of renal function tests. Urinary catalase and urinary protein tests were performed on all urine samples. These were uniformly negative for patients 1, 2, 3 and 4. Patient 5 (dose = 42 μg/kg) showed normal catalase but

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Table 4.3. Collection time and urine sample uranium content in percent dose for Rochester patients. (Taken from Bassett et al., 1948)

Patient 1		Patient 2		Patient 3	
hours post-inj.	dose %	hours post-inj.	dose %	hours post-inj.	dose %
3	53.3	0.5	26.2	1.5	34.8
4	9.7	2.1	21.2	6.3	26.0
9	15.5	5.3	20.0	9.8	4.2
11	2.1	7.8	4.9	18.8	3.8
21	1.8	9.5	3.9	23	0.48
46	2.3	16.8	6.6	47	1.14
69	0.97	22.0	2.0	71	0.55
93	<0.20	46	1.8	95	0.30
117	<0.20	70	0.34	119	0.26
141	<0.07	94	0.14	143	0.13
		118	<0.06	167	0.12
		142	<0.06	191	<0.1
				215	<0.1

Patient 4		Patient 5		Patient 6 (1st inj.)	
hours post-inj.	dose %	hours post-inj.	dose %	hours post-inj.	dose %
3.3	23.4	6.2	52.5	0.4	1.2
5.1	12.4	7.8	9.3	2.5	21.8
9.9	17.5	11.8	4.3	5.4	17.2
13.2	5.0	14.0	2.8	7.8	15.3
16.2	4.6	15.8	1.6	9.8	7.7
21	2.8	19.3	1.6	12.1	5.7
45	3.1	22.3	1.06	14.7	3.7
69	1.1	46	1.75	17.9	2.6
93	0.37	70	0.14	21.1	1.56
117	0.21	94	0.04	22	0.86
140	0.19			46	5.24
165	0.12			70	1.81
189	0.12			94	1.81
213	<0.04			118	1.00
237	0.10			142	0.75
261	0.10			166	0.42
285	<0.06			190	0.46
309	<0.04			214	0.44
333	0.04			238	0.44
357	0.10			262	0.46
381	0.03			286	0.41
405	<0.03			310	0.27
				334	<0.17

a trace of protein appeared in the fourth day urine sample. The authors state "it is suspected that this was a chance observation and without significance as far as uranium is concerned". No follow-up was possible because the patient insisted on being discharged from the hospital. Patient 6 (dose = 70.9 μg/kg; 3.9 mg uranium total) showed slightly higher catalase and traces of protein in the fifth and sixth day urinary samples. The authors remark "while it cannot be stated that either test is unequivocally positive, it would seem advisable that any further increase in the dose should be made in small increments".

Urinary Excretion of Hexavalent Uranium. Table 4.3 lists the urinary uranium results for the six patients. Fig. 4.1 plots the administered dose taken as 100 per-

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·tient 3	
›urs ›et-inj.	dose %
1.5	34.8
6.3	26.0
9.8	4.2
5.8	3.8
3	0.48
7	1.14
1	0.55
5	0.30
9	0.26
3	0.13
7	0.12
1	<0.1
5	<0.1

.tient 6 (1st inj.)	
urs ·t-inj.	dose %
.4	1.2
.5	21.8
.4	17.2
.8	15.3
.8	7.7
.1	5.7
.7	3.7
.9	2.6
.1	1.56
	0.86
	5.24
	1.81
	1.81
	1.00
	0.75
	0.42
	0.46
	0.44
	0.44
	0.46
	0.41
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	<0.17

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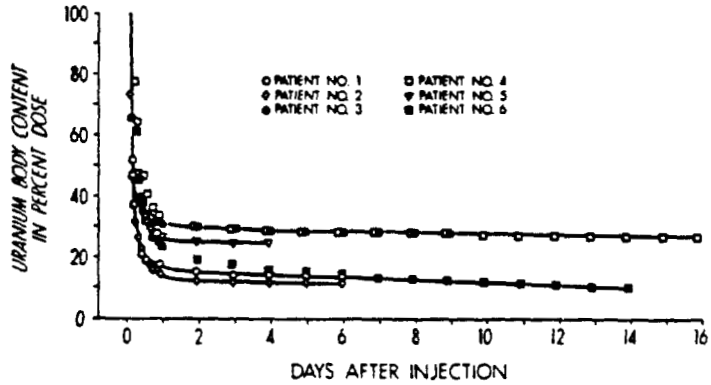

Fig. 4.1. Uranium body content after a single intravenous injection of six patients (Rochester experiment)

cent minus the cumulative urinary excretion in percent as a function of time after dose administration up to the termination of urinary collection. In the figure the ordinate is listed as percent body content because the fecal excretion of intravenous hexavalent uranium was found to be negligible compared to urinary excretion. For example, over the period of the experiment, Patient 1 excreted 86 percent via the urine and less than 0.87 percent via the feces. Consideration of Fig. 4.1 shows that the urinary excretion pattern is characterized by a very rapid early excretion so that 50 percent of the dose is excreted in from 3 to 10 hours and from 70 to 86 percent is excreted in 24 hours. The remaining 13 to 30 percent is excreted very slowly, so slowly in fact that the analytical sensitivity is frequently insufficient to measure the activity in the sample aliquot as reference to Table 4.3 indicates. For this reason, as well as the relatively short duration of the experimental periods, the loss rate from this slowly turning over compartment (assumed by BASSETT et al. to be bone) is poorly determined by these experiments.

Uranium in Fecal Samples and in Blood. As stated above urinary excretion was almost the exclusive route or uranium body loss. Fecal samples from the first day on contained insufficient amounts to be measured by the analytical technique used, i.e. were less than from 0.1 to 0.3 percent dose, the sample limit being a function of sample size and aliquot size. Two blood samples were analyzed for uranium. Twenty-eight ml of blood drawn from patient 4 eight minutes after administration of 1.92 mg U contained 1.2 μg U. Assuming a total blood volume of 5000 ml (0.078 times body weight), it may be calculated that at this time only 11 percent of the dose remained in the circulating blood. A blood sample of 26 ml was withdrawn from patient 6 at 16 minutes after administration of 3.91 mg U and found to contain 2.7 μg of U[2]. Assuming a total blood volume of 4000 ml (0.078 times body weight), it was again found that about 11 percent of the dose was in the circulating blood.

Procedures Designed to Alter the Excretion Rate. Three experiments were performed. It was estimated that patient 4, 12 days post-administration, retained 535 micrograms of uranium. Inasmuch as hexavalent uranium complexes readily with citrate an attempt was made to mobilize the residual uranium by giving 2000 ml of a solution containing 9.2 g sodium citrate and 2.2 g citric acid by

2 Additional data not included in UR-37, available to the authors through the courtesy of Dr. W. F. BALE.

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intravenous drip. This procedure did not increase the rate of urinary excretion of uranium. The concentration of citrate in the urine increased very little suggesting that the citrate was metabolized rather than excreted.

Patient 6 made himself available for further studies after conclusion of the initial experimental period. At 12 days post-dose he retained about 10 percent of the injected uranium. At this time he was rendered acidotic by giving 8 g of ammonium chloride daily for 3 days, 12 g daily on the fourth and fifth days. On the fifth day he was given a second intravenous dose of 3.17 mg hexavalent uranium. The dose of ammonium chloride was reduced to 4 mg a day and discontinued after the ninth day. Measurements of CO_2 content of the blood serum on the day 5, 6, 9 and 13 showed a steady increase up to 70 volumes percent. This procedure had the effect of slowing down the initial rate of urinary uranium excretion but at 15 days post-injection the total amount of uranium excreted was the same for the normal and the acidotic condition.

At the conclusion of these two tests it was calculated that the total amount retained was about 1.17 mg uranium. In an attempt to mobilize this uranium dietary calcium was reduced to 0.2 g per day and gradually increasing doses of dihydrotachysterol (AT-10) were simultaneously administered. The maximum AT-10 dosage was 7.5 mg a day continued for 18 days. The urinary excretion of calcium was increased three times, but urinary phosphorus and urinary uranium were unchanged.

The Mechanism of Excretion of Hexavalent Uranium. The authors interpret their result in terms of the mechanism of excretion suggested by DOUNCE (VOEGTLIN and HODGE, 1949, chap. 15) and depending on animal results. It is proposed that in the blood where there is a large excess of uranium, about 60 percent of U(VI) forms a complex of the type $UO_2(CO_3)_2$. The diffusible bicarbonate complex is filtered at the glomerulus. In the tubule water is reabsorbed as well as base and acid carbonate. The resulting acidification leads to the partial breakdown of the uranium bicarbonate complex permitting either uranium combination with the cell protein of the tubules which in excess may produce injury, or forming a temporary binding complex formation with organic acids or phosphate in which case it is excreted directly. In subject 6 the administration of ammonium chloride created a highly acid urine, reducing the available bicarbonate and favoring the temporary binding of uranium by the tubular cell protein thus slowing up the rate of excretion.

2. The Boston Intravenous Injection Experiment

(STRUXNESS, LUESSENHOP, BERNARD and GALLIMORE, 1956; LUESSENHOP, GALLIMORE, SWEET, STRUXNESS and ROBINSON, 1958; BERNARD, MUIR, and ROYSTER, 1956)

A collaborative experiment involving the intravenous injection of uranium was performed by members of the Health Physics Division of the Oak Ridge National Laboratory and Dr. WILLIAM H. SWEET of the Massachusetts General and the Veterans Administration Hospitals in Boston. Although the primary justification for these experimental injections of uranium in man was the possible value in neutron capture therapy (SWEET and JAVID, 1952), the Oak Ridge group was interested in the study of the tissue distribution and excretion of uranium as it applied to calculation of protection criteria for uranium workers. The preparation of the dose and the analyses for uranium in excreta and tissues were done in Oak Ridge.

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Table 4.4. Patient data and urinary excretion of intravenous uranium. (Data from LUESSENHOP et al., 1958; STRUXNESS et al., 1956)

Patient	Age yr	Sex	wt. kg	Dose[a] μg/kg	Excretion percent dose		Survival post-injection days
					24 h	total	
1	26	m	55.9	99	59.4	69	2.5
2	47	m	57.4	103	78.0	92	74
3	34	m	60.0	72	83.8	98	566
4	63	f	67.7	165	77.2	85	136
5	39	m	55.9	283	66.5	85	139
6	60	m	56.7[b]	907	49.1	63	18
7	—	—	71.8[b]	573[b]	20.0	68[b]	228[b]
8	—	m	63.2[b]	700[b]	16.9	57[b]	21

[a] These values differ slightly from those listed by LUESSENHOP et al. (1958). We have assumed that the body weights and total dose administered as listed by them are correct. If these numbers are used, the values listed above are obtained.
[b] These data were kindly provided by Dr. S. R. BERNARD.

The eight patients forming the subject group were in the terminal phase of severe central nervous system disease. The ages were 26 to 63 years. At the time of injection all patients except one were in coma and were receiving the usual hospital care consisting of frequent turning, skin care, gastric tube feedings, catheter drainage, and tracheal suction when necessary.

Uranyl nitrate solutions, enriched in ^{235}U and ^{234}U, were prepared and administered intravenously to the first six patients. Patients 7 and 8 were similarly injected with a solution of tetravalent uranium as UCl_4. The amounts received by each patient are listed in Table 4.4.

Collection and Analysis of Samples. One to 3 ml blood were taken by phlebotomy in the arm not used for the uranium injection at the rate of one sample each hour for the first 24 hours, one sample each 12 hours for several weeks, one sample each 24 hours until transfer from the hospital. Bone biopsy specimen to determine initial uptake were taken from the anterior tibia with a 0.5 in. trephine. Urine specimes were collected hourly from indwelling catheters for the first day post-injection, and at 12-hour intervals for 2 to 4 weeks. Thereafter 12-hour duration spot collections were made at 1 to 4 week intervals. Total collection of feces was made for the duration of the patients' hospital stay. Autopsy samples were obtained on patients 1, 2, 3, 5, 6 and 8. Twenty-one different organs or tissues were collected. Triplicate aliquots of each urine specimen were wet ashed, evaporated, made up to volume and electroplated for alpha particle counting. Blood samples were analyzed in generally the same way as urine samples. Tissue samples less than 2 g wet weight were dry ashed at 600° C for 24 hours, dissolved in 0.1 N nitric acid, and the entire sample electroplated and counted in an alpha particle counter. Feces, bone, and tissue samples greater than 2 g wet weight were dry ashed at 600° C for 24 hours. The resulting ash was weighed and uranium analysis was performed using the aluminum nitrate/diethyl ether extraction procedure with evaporation on an stainless steel planchet for alpha counting.

Urinary and Fecal Excretion. Table 4.4 presents data on the patients' administered dose, the percent dose excreted in 24 hours, and total urinary excretion. The largest amount measured in a single fecal sample was 0.03 percent dose

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Table 4.5. Percent of injected dose per standard man organ or tissue estimated from autopsy results. (Taken from BERNARD and STRUXNESS, 1957: their Table IV abridged)

Patient no.	1	6	2	5	3	8[a]
Bone	10.0	4.9	1.4	0.6	1.3	14.4
Kidney	16.6	7.2	0.7	1.2	0.4	1.1
All other tissues and organs	8.4	5.9	1.9	1.2	0.3	15.7
Bone tibia biopsies 0–48 hours average % dose per 7000 g	9.1	6.4	6.5	3.9	4.2	1.3

[a] This patient was injected with uranium tetrachloride.

and the usual sample contained much less. The authors find the rates of urinary excretion of uranium are best represented as power functions and the best line through all the data describes the equation: $\%/\text{hr} = 34.3\ t^{-1.5}$. The power function fails at times shorter than 5 hours post-injection.

Loss from the Blood. The large number of blood samples collected in this experiment permitted the construction of detailed blood disappearance curves. It was found that at six minutes the blood contained about 33 percent of the injected dose and that 99 percent had left the blood at 20 hours.

The Minimum Single Dose Resulting in Kidney Damage. LUESSENHOP, the physician who reviewed the battery of clinical tests employed to evaluate kidney function in these patients, finds that the minimal dose to produce catalasuria and albuminuria is of the order of 0.1 mg per kg body weight (LUESSENHOP et al., 1958). When the patients came at autopsy the acute tubular damage was no longer visible and the histopathological findings were said to be comparable to those often seen in terminal patients.

Tissue Distribution of Uranium. The autopsy results on patients receiving hexavalent uranium are summarily listed in Table 4.5. The original data including all measurements show that apart from the bone and kidney there are no significant concentrations of uranium in any of the 21 tissues and organs sampled. The autopsy on subject 8 who received tetravalent uranium shows 9.2 percent in the liver and 5.6 percent in the spleen.

3. Experiments Using Uranium Injections to Evaluate Skeletal Metabolic Disorders

(TEREPKA et al., 1964)

TEREPKA et al. injected intravenously 30 micrograms hexavalent natural uranium per kg in three control patients without clinical, laboratory or x-ray evidence of bone disease and seven patients with a variety of bone disorders. The objective was to develop a means of evaluating the metabolic status of the skeleton. The rationale depended on earlier animal evidence that about 70 percent of a single injection of soluble uranium was rapidly cleared via urinary excretion and that of the amount retained "virtually all could be accounted for in bone. Both *in vivo* and *in vitro* studies indicated that the uranyl ion forms a stable linkage, probably with phosphate groups on the surface of hydroxyapatite crystals". The amounts of uranium excreted in the urine during the early post-injection period are listed in Table 4.6. The results are interpreted by TEREPKA et al. as showing that uranium retention is a function of the relative quantity of available or exchangeable bone. Experiments (not included in the table) which

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Table 4.6. Urinary excretion after intravenous injection of uranyl nitrate. (Taken from TEREPKA et al., 1964)

Patient				Urinary excretion in % dose/24 h					
	age	sex	condition	day 1	day 2	day 3	day 4	day 5	day 6
CM	53	m	normal	61.5	3.8	1.5	0.7	0.6	0.4
RW	53	m	normal	64.3	3.1	1.5	0.6	0.5	—
JP	72	m	normal	61.5	6.1	2.1	1.3	0.4	0.4
CW	53	m	Paget's disease	16.0	5.6	1.1	0.6	0.6	0.6
CW	53	m	Paget's disease[a]	18.6	7.2	1.5	—	—	—
CS	58	m	hyperparathyroid	31.0	—	—	—	—	—
AK	71	f	hyperparathyroid	63.3	6.9	—	—	—	—
MC	60	f	osteomalacia	34.2	5.0	2.6	2.1	1.3	1.1
JL	62	m	osteomalacia	32.6	7.1	—	—	—	—
MC	74	f	osteoporosis	59.5	6.3	1.9	1.2	0.9	0.5
AH	81	f	osteoporosis	60.1	6.1	2.1	0.9	0.8	0.6

[a] After treatment with Prednisone (5 mg twice daily).

unsuccessfully attempted to mobilize stored uranium by administration of parathyroid extract are believed to suggest that either (1) the uranium was deposited in areas of bone not affected by the resorbtive process or (2) that there is a cation specificity to the effects of parathyroid hormone. The authors held forth the possibility that "the marked difference between bone uptake and release of uranium and calcium may help to distinguish the relative contribution of bone accretion and bone resorption to the development of metabolic bone disease in man".

4. Interpretation of the Intravenous Experiments

Excretion. The three sets of experiments show excellent agreement where comparisons are possible. The 24 hour urinary excretion of hexavalent uranium yields an average of all values (except patient 6 in the Boston experiment) of 72.1 ± 8.3 percent dose. There is no apparent correlation with patient age or sex. The Boston data appear to indicate a reduced rate of excretion with increase in dose size, but no such relationship appears in the Rochester data. It is perhaps somewhat surprising that the two sets of data do not show greater differences. The Rochester patients were ambulatory in the metabolism ward and were not seriously ill, whereas the patients in the Boston study were with one exception in coma at the time of the injection.

The Minimal Dose to Produce Kidney Injury. Here again, the two sets of data are in reasonable agreement. The Rochester group found that transient injury was produced at their highest dose of 70.9 μg per kilogram and from the Boston experiment we learn that single doses of about 100 μg per kilogram produced catalasuria and proteinuria. From his consideration of the Boston data, and deriving a scaling factor from published findings on the rabbit, LUESSENHOP estimates (LUESSENHOP et al., 1958) the lethal intravenous dose for man at about 1 mg uranium per kilogram.

Tissue Distribution of Uranium. Although Terepka's data indicate that the metabolic status of the skeleton has a marked influence on the urinary excretion of uranium and by inference that the skeleton of normal man is an important repository for uranium, they do not include specific tissue distribution values. The Boston data on tissue distribution, in a quite general way, confirmed the

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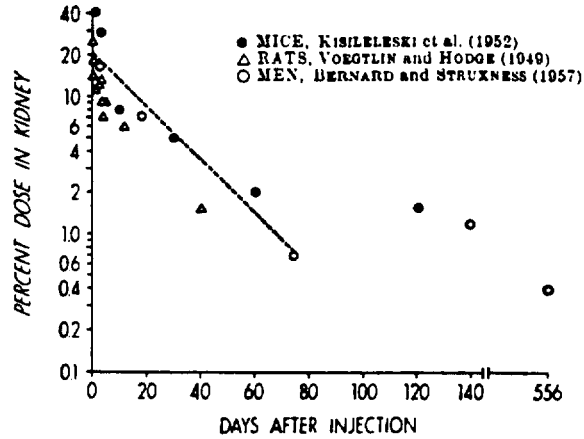

Fig. 4.2. Comparison of the uranium content of the kidney in several mammalian species after a single injection of uranium

pattern which might have been expected from the animal data: the intravenous hexavalent uranium which is not rapidly excreted deposits in the kidney and in the bone; when tetravalent uranium was introduced into the blood stream deposition in the kidney was reduced, and appreciable retention was observed in the liver and spleen. For the prediction of steady-state organ burdens after chronic occupational exposure by use of single exposure data, it is necessary to know the rate at which uranium is lost by the organ. Manipulation of the Boston data to this end introduces, in addition to the uncertainty caused by one subject per time point, uncertainties associated with the relatively rapid rate of introduction of massive doses of uranium and the parlous clinical condition of the subjects. It is well known that bed patients display a negative calcium balance and impaired circulation. Although these uncertainties are recognized, the Boston data are unique and afford the only opportunity to compare loss rates of uranium from the bone and kidney of man with similar animal data. BERNARD (1948) working with the Boston data, estimated biological half-times of 300 days for both bone and kidney. The value of 300 days for bone does not represent any change from that cited in N.B.S. Handbook 52 (1953) and based on animal data. On the other hand, acceptance of the 300 day half-life for the kidney would represent a substantial departure from the 15-day half-life currently in use by the NCRP and ICRP. From close consideration of the evidence it would appear that the existing data on animals and on man show no real differences and that the issue is one of interpretation rather than a conflict in the experimental findings. Fig. 4.2 is presented to support this view.

B. Oral Administration of Uranium

1. Use as a Therapeutic Agent

It is reported that oral administration of uranyl nitrate in small doses was used as early as 1851 to treat diabetes. Dr. SAMUEL WEST stimulated renewed medical interest in this form of treatment by two papers (1895, 1896) in which he described the alleviation of symptoms in 8 cases of diabetes mellitus treated with uranium. The motivation for using uranium calls to mind Mallory's explana-

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tion[3] of why he proposed to climb Mt. Everest. As West explains in his first paper "Some time ago my colleague at St. Bartholomew's Hospital, Dr. W. J. RUSSELL, the lecturer in chemistry, placed in my hand a double chloride of quinine and uranium, and suggested that I should try its action on disease". Early in his use of the drug West decided that uranyl nitrate was as effective as the double chloride of uranium and quinine. The regimen that he adopted was to begin by administering small doses, 30–60 mg U as uranyl nitrate in water, 2 or 3 times per day after meals, and as tolerance developed to increase this amount until beneficial results were observed. He notes that doses as high as 1.8 gram U per day were tolerated by the patient without gastric distress. He found in most cases that the sugar in the urine, the volume of urine, and the patients' thirst were reduced. When treatment was stopped the patients reverted to their pre-treatment status.

The findings of WEST were in general supported by DUNCAN (1897), BOND (1898), TYLECOTE (1904) and by WILCOX (1915). BOND's Case 9, a man of 62 years of age weighing 118 kg, is particularly notable because of the dose size. He was started at a dose of 185 mg U, 3 times per day and worked up to 925 mg U, 3 times per day, a dosage rate that was continued for one year. A sample of his urine taken during the latter part of the year was negative for uranium.

Experiments on animals had demonstrated that intravenously injected uranium in sufficiently high amounts could produce severe kidney injury. The physicians who made use of uranium as a therapeutic agent were aware of this work and their reports stress that the urine was examined for evidence of kidney injury and that none was found.

Medical opinion was not uniformly in support of this method of treatment [see, for example, the discussion following DUNCAN's paper (1897)] and although uranium was listed as a materia medica in the early 1900's, by the mid-thirties SOLLMANN (1936) was to advise that "The results are too indefinite to justify the further employment of so dangerous an agent". Quite apart from the merits of the treatment, the fact that these studies were made provides the interested toxicologist with data on a group of human subjects with a chronic exposure to oral uranium.

2. Experimental Ingestion by a Volunteer Subject

BUTTERWORTH (1955) published a paper examining the usefulness of analyzing the urine of workers for uranium as an exposure control measure. In this paper he included an account of a volunteer who ingested 1 gram uranyl nitrate (0.47 gram U) in 200 ml water in order to obtain data on uranium hazard evaluation. The results were dramatic. The person experienced rather violent vomiting, diarrhea, and slight albuminuria with a peak uranium urinary concentration of 8 mg U per liter (2 specimens of 30 ml). During the first week he excreted in his urine 2.5 mg U. Assuming a renal excretion of 66 percent of the uranium absorbed from the gut, it was estimated by the author that the subject absorbed at least 1 percent of the dose. Within 24 hours the subject's clinical recovery was complete. This experimental result created attention because the gut absorption factor for uranium then accepted by the ICRP and NCRP committees was 0.01 percent (based on rat data) and not 1 percent.

Regardless of the reservations which might properly be attached to an experimental result associated with such far-reaching gastrointestinal disturbances, it did, at that time, constitute the only uranium absorption data on man. As a

3 "Because it's there."

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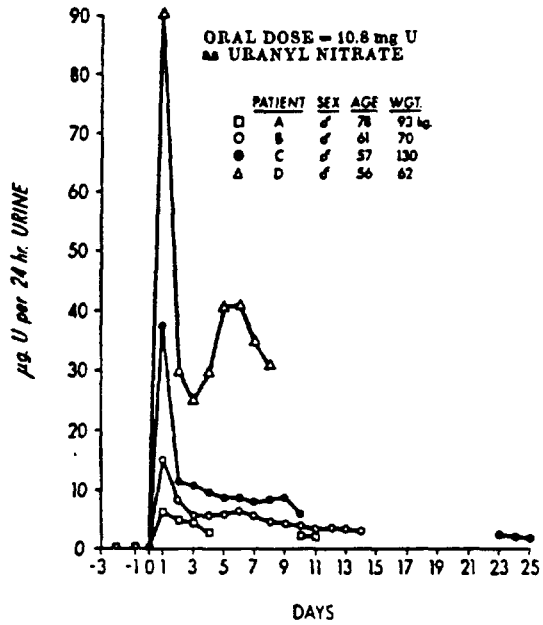

Fig. 4.3

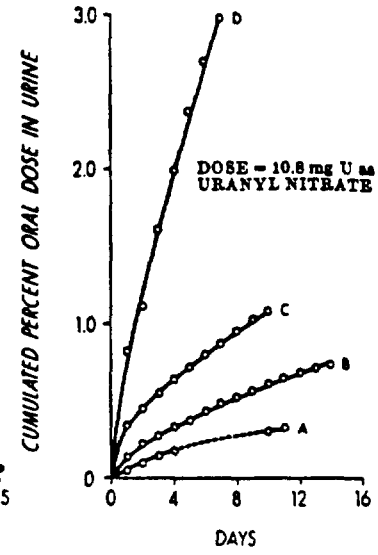

Fig. 4.4

Fig. 4.3. The rate of urinary excretion after oral administration of uranyl nitrate to 4 human subjects

Fig. 4.4. The cumulative amount of uranium excreted in the urine after oral administration of uranyl nitrate to 4 human subjects

consequence of this finding, supported by experimental studies (FISH et al., 1960) on 10 dogs who received a single oral dose of UO_2F_2 in water and yielded an average absorption factor of 1.55 percent, the ICRP in Publication 6 (1964) increased the absorption factor from 1×10^{-4} to 1×10^{-3} for uranium.

3. Hospital Study on Oral Absorption of Uranyl Nitrate

HURSH et al. (1969) conducted an oral absorption study on four hospital patients. The patient selection criteria were (1) no known gastrointestinal disorder, (2) normal kidney function, and (3) availability for a minimum of 7 days. The selected subjects were transferred to the Clinical Research Unit for the testing period. Each subject received prior to his breakfast an oral dose of 10.8 mg U as uranyl nitrate hexahydrate dissolved in 100 ml of Coca-Cola. Urine and fecal samples were collected and analyzed for uranium. A pH measurement was made on the urine samples soon after collection and all samples were examined for protein. The patients reported no subjective symptoms and no protein was found in any of the urine samples. The results of the uranium determinations appear in Figs. 4.3 and 4.4. In the original experimental plan, only urine samples were to be collected[4]. The rationale behind this procedure was to rely on data from the

4 It might appear that the straightforward way of determining the absorbed fraction would be to collect all the feces and to subtract the total amount of uranium found therein from the administered dose. However, it must be remembered that the experimenters had good reason to anticipate that the absorbed fraction would be of the order of 1 percent or less and that they were aware of the variety of experimental and analytic errors which would conspire to defeat any attempt to determine the administered dose and the fecal uranium content to the precision necessary to determine such a small difference.

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B[a]	[illegible]					[illegible]	
C	(— —	86)	(— 12)	(— —	— —	1.7)	99.7
D[b]	(— 3.0)	(— 36.1)	(15.7)	(— 17.6)	(— 19.4)		91.8

[a] Spot collections only were made for patient B. Total collections were made for patients C and D; the collection period is indicated by brackets.
[b] One sample between 0 and 3 days missed.

intravenous experiments on man which indicated that a reasonably constant fraction, about 70 percent, of the absorbed uranium would be promptly excreted in the urine during the first 24 hours. Measurements of urinary uranium would therefore permit the ready calculation of the total amount absorbed. After the data from the first patient (patient A, Fig. 4.3) became available, it was apparent that, contrary to expectation, appreciable amounts of uranium continued to be excreted in the urine for a period of many days[5]. In an effort to assist in the interpretation of this finding, fecal samples were collected on the remaining three subjects. The results of the analyses of these samples are presented in Table 4.7.

It may be noted that the cumulative urinary loss had not reached a plateau for any subject at the end of the experimental period and that, therefore, the prospective total urinary loss can be estimated to be in excess of 0.3, 0.7, 1.1 and 3.0 percent dose for patients A to D respectively. Inasmuch as about one-third of the amount absorbed is taken up by the skeleton and the kidney, these numbers should be multiplied by 1.5 to yield minimum estimates of the uranium absorbed.

It is suggested by the authors that if the prolonged urinary excretion has the corollary of a prolonged period of uranium absorption, the radiological hazard to the gut cannot properly be calculated in terms of the more rapid passage of ingested food as is done in the current ICRP gastrointestinal model.

4. Interpretation of the Oral Experiments

The reported results of oral dosing of diabetic patients include three claims that need to be critically evaluated: that despite the large doses of uranium (1) gastrointestinal disturbances did not occur, (2) no uranium appeared in the urine, (3) no kidney injury occurred. None of these claims are supported by the scanty modern experimental data cited above in this section. Of the series of 22 cases total presented by West (1895, 1896), Duncan (1897), and Bond (1898), one patient received single doses of 0.91 g, two patients 0.61 g and three patients 0.46 g U repeated three times daily and continued for weeks, months, or as long as one year[6], whereas Butterworth's volunteer received a single dose of 0.47 g U and displayed severe gastrointestinal symptoms. Two explanations suggest themselves. The medical practice of beginning with small doses and increasing the dose until a beneficial effect was produced may have created a sort of habituation so that large doses could be tolerated with no gastric symptoms. Alternatively it may be supposed that the volunteer subject was susceptible to this

5 This pattern was not followed by Butterworth's subject. In that case 88% of the total urinary loss for the first week occurred on the first day. It may be assumed that the physiological processes of vomiting and diarrhea made a clean sweep of the gastrointestinal tract.
6 Wilcox's (1917) larger series of 84 treated patients are all of such low dosage as not to come into question.

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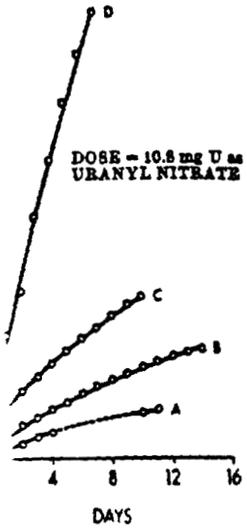

Fig. 4.4
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Table 4.7. Percent dose in feces on day as designated. (Taken from HURSH et al., 1969)

Patient	−2	−1	0	1	2	3	4	5	6	7	8	9	Cumulative
B[a]	0.002	0.004										0.22	
C			(—	—	86)	(—	12)	(—	—	—	—	1.7)	99.7
D[b]			(—	3.0)	(—	36.1)	(15.7)	(—	17.6)	(—	19.4)		91.8

[a] Spot collections only were made for patient B. Total collections were made for patients C and D; the collection period is indicated by brackets.
[b] One sample between 0 and 3 days missed.

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[6] WILCOX's (1917) larger series of 84 treated patients are all of such low dosage as not to come into question.

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manifestation of uranium toxicity and that if an equally large number of normal volunteers had been tested, individuals would be found displaying a tolerance comparable with that of the patient group. It should be noted that the "conditioned" patients were not uniformly free of gastrointestinal disturbances. Two of WEST's 9 cases (at 0.1 g and 0.15 g single dose) and one of DUNCAN's 5 cases (at 0.46 g single dose) reported dyspepsia and loose bowels.

Either explanation must take the conditions of administration into account. The patients received their nostrums directly after meals in the hopeful, trusting aura of the patient-physician relationship. The volunteer ingested his dose an hour or so after breakfast and probably appreciated he was drinking a toxic substance of no direct benefit to his health. Any choice between these two explanations must be intuitive rather than rational in the absence of adequate experimental data.

The second claim, i.e. that the urine contained no uranium, can be dealt with more satisfactorily. Modern data will be used to predict an upper limit for the daily uranium urinary excretion of BOND's Case 9 who received a total daily oral dose of 2.7 grams, as follows. Assuming a gut absorption factor of 0.05 and that 0.70 of the uranium passing into the circulation is excreted per day we might expect 95 mg uranium in one day's urine. BOND (1898) states that the daily urinary volume of this patient was about 76 ounces (2.2 liters). The concentration of uranium would therefore be about 4.3×10^{-5} grams per ml urine. It is apparent that an analytical method that could "readily detect 1 part in 2000" (BOND's comment on the chemical method for uranium as used at that time) would fail to detect the concentration of uranium predicted for BOND's exceptionally high-dose patient.

While the above calculation may serve to press the point that the failure to detect uranium in the urine was caused by insensitivity of the then current analytical methods it is almost certainly an overestimate.

The postulated 135 mg U per day (or $135/118 = 1.14$ mg/kg) passing into the circulation can be compared with the kidney injury threshold of about 0.1 mg/kg derived from the intravenous experimental studies and the assumed systemic intake of about 5 mg absorbed from the gut by BUTTERWORTH's volunteer subject.

Even if a more likely 1 percent absorption factor is assumed the contrast remains between the severe kidney injury to be expected based on data from the intravenous and oral experiments and the reported absence of albuminuria in the substantial number of medically treated patients who ingested amounts equal to or greater than 0.9 grams uranium per day for extended periods. This is yet more noteworthy in that, to the extent that the diabetic patients as a group had a chronically low blood bicarbonate reserve, the kidneys would be expected to fix a greater fraction of the available uranium and to suffer a more severe injury. It is plausible that the practice of gradually increasing the dose produced a tolerance in the medically treated subjects. This could be achieved either by a mechanism which reduced absorption from the gut or which in some way protected the kidney.

Both decreased absorption (CLOETTA, 1906; JOACHIMOGLU, 1916) and increased excretion (HAUSMANN, 1906) have been invoked to explain the habituation of the arsenic eaters of the Styrian mountains who are able to ingest once or twice weekly up to 0.3 g of arsenic trioxide, whereas 0.1 to 0.3 g is usually fatal. Perhaps more immediately to the point are the animal experiments demonstrating that a conditioning series of sublethal adminstrations of uranium will protect against the killing effect of a single large dose. HAVEN (VOEGTLIN and HODGE, 1949, chap. 12) finds that the kidneys of tolerant rats retain less uranium

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and concludes that elevated levels of citric acid in the kidney tubule may account for acquired uranium tolerance. Earlier experimenters (HUNTER, 1928; MACNIDER, 1929) studied the tolerant kidney histologically and concluded that normal tubular epithelial cells were destroyed by the conditioning doses of uranium and replaced by a resistant epithelial cell type.

An important aspect of the animal experiments is that in order to produce tolerance, it was found necessary that the conditioning doses be high enough to produce some kidney injury. If the same rule holds for man, it may be inferred that the demonstration of tolerance in animals and the likelihood of its occurrence in man under some conditions does not warrant that it will be an ameliorating factor in the chronic exposure of uranium workers, where by intent the daily dose is regulated so that even transient kidney injury will not occur.

C. Inhalation of Uranium

1. Experimental Clearance of Uranium Dust from the Human Body (HARRIS, 1961)

Examination of published reports have revealed only one experiment involving the planned inhalation of uranium compounds by man. A single experimental subject was exposed for 17 short periods to inhalation of first UO_3 (12 periods), and later UF_4 (5 periods) over a total elapsed time of 24 days. The design of the experiment and the interpretation of the results were closely related to the reason for performing the experiment. Harris starts from the position "Our experience in the uranium industry has been that, although workers appear to be exposed to dust concentrations which are very much higher than those which experiment had determined should produce illness, such illness has not been seen". He argues that a possible cause might be the characteristically larger average particle size of industrial dust as compared to that used for the animal experiments relating exposure and injury. Such a larger particle size would favor deposition in the naso-pharyngeal region and the other ciliated airways, and consequently a smaller fraction would be deposited in the parenchyma of the lung. The uranium dust deposited in the ciliated passages would be escalated, swallowed and passed into the gastrointestinal tract. Because even so-called "soluble" uranium is poorly absorbed from the gut only a few percent would find its way into the systemic circulation and the remainder would be excreted in the feces. Harris and his colleagues at the Health and Safety Laboratory, New York Operations Office of the AEC, pursued this interpretation by developing several dust sampling devices designed to separate dust into the two fractions, *viz.* that, which because of its inertial and aerodynamic properties, would deposit in the upper respiratory tract and that which would deposit in the lung parenchyma. In the report (HARRIS, 1961) it is stated that a preliminary check on several industrial processes in a uranium plant using one of these dust sampling devices indicated that 95–99 percent of the total dust concentration would be removed by the upper respiratory system. The objective of the experiment to be described was to compare the prediction of the device with human data in an actual inhalation experiment.

Experimental Design. The schematic drawing of the arrangement for inhalation exposure is reproduced from the original paper and appears as Fig. 4.5. The subject, using a valved face mask, inhaled UO_3 for 12 brief periods spaced in time as indicated in Table 4.8. About 7 days after the last UO_3 exposure another series was begun in which the subject inhaled UF_4 for five periods in the space of 3 days.

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and it is necessarily always administered with food. On the technical side, the value for the daily dietary input is supported by the U.S.A., the U.K., and the Japanese data; the urinary output (U.S.A.) is based on samples from 37 subjects and the urinary output (U.K.) is based on 300 samples.

2. Rate Constant for Whole Body Loss

The rate of loss of systemic uranium (as distinct from that in the lung or gut) may be also estimated from these data. Grounded in the same central assumption that the urinary loss is the only important excretory route, the fraction of the whole body burden excreted per day becomes 0.154/80 (U.S.A. data) and 0.380/100 (U.K. data) or 1.9×10^{-3} day^{-1} and 3.8×10^{-3} day^{-1} as the respective loss constants. The corresponding half-times are 360 days and 180 days. The value listed in ICRP Publication 2 is 100 days. The body burdens entered in Table 4.16 and used here are estimates and depend primarily on the average uranium content of bone which is based on 63 sample measurements (U.K. data) and 8 sample measurements (U.S.A. data). It is to be hoped that the experimental interest in collecting data on the turnover of natural uranium will continue and that these estimates may be supported or modified in the future.

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